The representative preparation of 2-deoxy-2-fluoro-D-arabinose 5-phosphate (**6**) was carried out as shown in Scheme II. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose (**1**) was first converted to the D-allose derivative **2**[6] which upon reaction with (diethylamino) sulfur trifluoride (DAST)[7] in methylene chloride and pyridine was transformed to the diisopropylidene derivative **3**. The isopropylidene groups were removed by hydrolysis with Dowex 50 (H^+) in water to yield 3-deoxy-3-fluoro-D-glucose (**4**): mp 114–115 °C (lit.[8] mp 112–113 °C); $[\alpha]_D^{20}$ +6.5° (*c* 1, H_2O) (lit.[1] $[\alpha]$ +6.4°, *c* 1, H_2O). Compound **4** (20 mmol) in aqueous solution (100 mL, pH 7.0) was phosphorylated at the 6 position to give **5** by ATP (0.2 mmol) catalyzed by yeast hexokinase (246 units, immobilized in 5 mL of polyacrylamide gels) coupled with a cofactor regeneration system containing immobilized pyruvate kinase (315 units, 3 mL gels) and phosphoenolpyruvate (22 mmol).[5] The conditions are essentially the same as those reported previously.[9] HPLC and enzyme analyses[10] indicated that the reaction was complete in 7.5 days. Compound **5** was isolated as a barium salt as described previously for the preparation of glucose 6-phosphate.[9] Enzymatic analysis indicated that 7.9 g of the product contains 87% of compound **5** as monobarium salts. At the conclusion of the reaction, each of the recovered enzyme activities was about 90% of their original activities and the turnover number for ATP was 100. Further oxidation of **5** (the barium ions were removed by treatment with Dowex 50) with 1.6 equiv of lead tetraacetate in acetic acid[11] gave compound **6** which was isolated in 62% yield as a sodium salt: $[\alpha]^{25}_D$ −72° (*c* 1.2, H_2O); ^1H NMR (90 MHz) of α form, δ (D_2O) 4.9 (d, $J_{1,2} = J_{2,3} = 0$, $J_{2,F} = 68$ Hz, H_2), 5.3 (d, 1 H, $J_{1,2} = 0$, $J_{1,F} = 9.5$ Hz, H_1); β form, 4.8 (m, $J_{2,F} = 68$ Hz, H_2), 5.2 (q, 1 H, $J_{1,2} = 4$ Hz, $J_{1,F} = 12$ Hz, H_1); ^{13}C NMR δ 63.1 (d, $J_{5,P} = 8$ Hz, C_5). The coupling patterns indicating the F group attached to C_2 and the P group attached to C_5 are consistent with those expected.

In summary, this study illustrates that the substrate specificity of hexokinase is wider than has been suggested in previous studies. This provides potentially critical information relating to the in vivo metabolic disposition of specific fluorinated sugar analogues. This work also suggested that hexokinase/pyruvate kinase should be useful catalysts in preparative synthesis of fluorinated sugar phosphates and analogues using the substrates shown in Scheme I. The phosphate group at the 5 position of pentoses enhances the attractiveness of these sugars as nucleotide precursors as the phosphate group locks the sugar in the furanose form. This allows the formation of a nucleotide having only the furanose configuration without the use of protecting groups.[12] Also, the phosphate group allows direct formation of a nucleotide eliminating the need for phosphorylation of a nucleoside intermediate. Another interesting point which deserves a brief comment is that the amino sugar **j** (Nojirimycin, a transition-state analogue of glucose which has been used as an antibiotic due to its strong inhibition on glycosidase enzymes)[13] is a reasonably good substrate for hexokinase and the phosphorylated derivative is also a good substrate for glucose-6-phosphate dehydrogenase.[14] One of the major concerns about the design and the use of antibiotic drugs is their effectiveness. The study shown here indicates that Norjirimycin might not be a long-lasting and effective antibiotic because it could be further metabolized and inactivated by enzymes in physiological systems.

Acknowledgment. Support of this research by the National Science Foundation (Grant CHE-8318217) is gratefully acknowledged. We thank H. M. Sweers for the preparation of Nojirimycin. D.G.D. thanks NSF for a graduate fellowship.

Supplementary Material Available: Experimental details for the preparation of compounds **e**, **j**, and **1-6** and their physical constants (8 pages). Ordering information is given on any current masthead page.

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(10) The concentration of **4** during the reaction was determined by HPLC analysis using a Waters μ-Bondapak/carbohydrate column (0.4 × 30 cm), with refractometer detection and aqueous acetonitrile (H_2O/CH_3CN, 25:75 v/v) as solvent. For a flow rate of 2 mL/min the retention time for **4** was 6.2 min. Compound **5** was determined enzymatically with glucose-6-phosphate dehydrogenase and NAD: Sessell, E. M.; Thomas, P. *Biochem. J.* **1973**, *131*, 83. For further physical data, see the supplementary material section.
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An Efficient Method for the Generation of *N*-Methylnitrones

Summary: *N*-Methylnitrones can be generated in good-to-excellent yields from aldehydes and ketones with a stoichiometric amount of *N*-methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine under very mild conditions and their formation, involving a bimolecular push–pull type mechanism, is discussed.

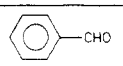
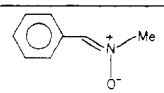
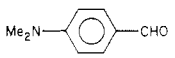
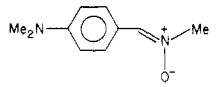
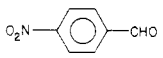
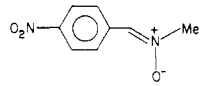
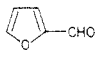
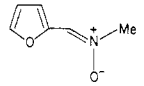
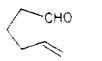
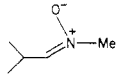
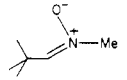
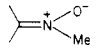
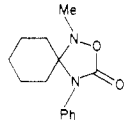
Sir: For our studies in the synthesis of natural products, we required a method to generate nitrones under very mild conditions[1] and to subsequently carry out nitrone–alkene cycloadditions in situ.[2] Herein, we report an extremely efficient procedure to prepare a variety of *N*-methylnitrones from *N*-methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine (**1**)[3] and aldehydes or ketones (Scheme I).

A typical procedure for the synthesis of *N*-methylnitrones is as follows. Treatment of benzaldehyde with a stoichiometric amount of **1** in benzene at 50 °C for 24

(1) For the synthesis of nitrones, see: (a) Tufariello, J. J. In "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 9. (b) Tennant, G. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 2, Part 8. (c) Delpierre, G. R.; Lamchen, M. *Q. Rev., Chem. Soc.* **1965**, *19*, 329. (d) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473. (e) After this manuscript was submitted, a paper concerning the preparation of nitrones from oxime derivatives was published, see: LeBel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331.
(2) For reviews of nitrone–alkene cycloadditions, see: (a) Padwa, A. In "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 12. (b) See ref 1a. (c) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (e) Black, D.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

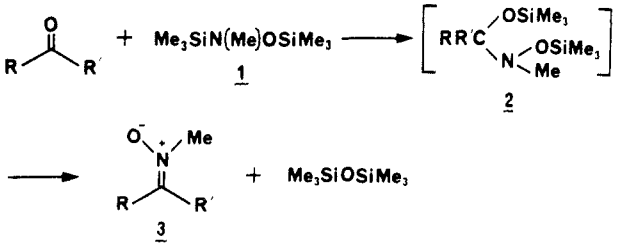
0022-3263/85/1950-5913$01.50/0

Table I. Formation of Nitrones from Aldehydes or Ketones with $Me_3SiN(Me)OSiMe_3$

entry	aldehyde or ketone[a]	conditions (temp/time + reagent[b])	nitrone or [3 + 2] adduct[c]	yield,[d,e] %
1		50 °C/24 h		97 (73-99)[18]
2		50 °C/28 h + Me_3SiOTf/rt/42 h		93 (63)[19]
3		50 °C/24 h + Me_3SiOTf/rt/48 h		98 (75-92)[14b,18a]
4		50 °C/18 h + Me_3SiOTf/rt/24 h		98 (NA)[14a]
5		50 °C/20 h + 80 °C/72 h		78 (40)[20]
6		50 °C/22 h		80 (NA)
7		50 °C/22 h		62 (NA)[21]
8		50 °C/24 h		78 (30)[22]
9		50 °C/24 h + PhN=C=O/rt/18 h		76 (25)[23]

[a] All reactions were run in anhydrous benzene at concentrations of 0.25-0.39 M. The ratio of aldehyde or ketone to $Me_3SiN(Me)OSiMe_3$ was 1:1 in all cases except entries 6-9. For isobutyraldehyde and acetone (entries 6 and 8), the carbonyl compounds were used as solvent. For trimethylacetaldehyde and cyclohexanone (entries 7 and 9), the ratio of carbonyl compound to $Me_3SiN(Me)OSiMe_3$ was 1.2:1. [b] Me_3SiOTf (0.03-0.04 equiv) was used as a catalyst and PhNCO (1.5 equiv) was used as a trapping agent. rt = room temperature. [c] The products were identified by comparison of spectral data and melting points (if available) to the literature data. [d] Numbers represent isolated yields. The solid products were isolated and purified by crystallization. [e] Numbers in parentheses represent literature yields.

Scheme I



h gave the nitrone and hexamethyldisiloxane. The volatiles were removed in vacuo by rotary evaporation, and the residue was recrystallized with ether/hexane. White crystals of *N*-methyl-α-phenylnitrone were obtained in 97% yield (mp 82–83 °C). Although this simple procedure works well in most cases, some modifications have been made for carbonyl compounds which show unique properties. Detailed conditions are listed in Table I.

Some important features of this method are noted: (a) In general, the highest yields are obtained when the ratio of **1** to aldehyde or ketone is 1:1. Use of excess **1** does not increase but rather decreases the amount of nitrone formed, while increasing the amount of silylated hemiaminal **2**. Conversely, the reaction proceeds well if excess aldehyde or ketone is used, which may be necessary in the case of volatile carbonyl compounds (entries 6–8). (b) Catalysts, such as trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) are necessary only in cases where the carbonyl group is under a strong electronic influence exerted by some functionality present (entries 2–4). (c) Although nitrones can be generated at lower temperatures, it is more efficient to carry out the reaction at 50 °C. (d) In addition to benzene, other solvents such as chloroform, dichloromethane, and toluene can be used to generate nitrones.

We have found in many cases[4] that formation of the intermediate hemiaminals **2** is much faster than their decomposition to the corresponding nitrones **3**. These hemiaminals are easily detected by NMR when the reaction is stopped before completion or when excess **1** is

(3) This reagent was prepared in 52% yield from the reaction of *N*-methylhydroxylamine hydrochloride (1.0 equiv) with chlorotrimethylsilane (2.0 equiv) and triethylamine (3.2 equiv) in ether at room temperature. For other methods, see: (a) Smrekar, O.; Wannagat, U. *Monatsh. Chem.* **1969**, *100*, 760. (b) West, R.; Boudjouk, P. *J. Am. Chem. Soc.* **1973**, *95*, 3987.

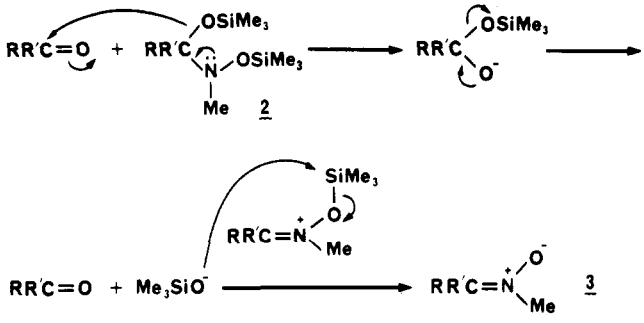
(4) These cases include benzaldehyde, *p*-(dimethylamino)benzaldehyde, *p*-nitrobenzaldehyde, 2-furaldehyde, 5-hexen-1-al, and cyclohexanone.

Table II. Reaction of Benzaldehyde and $Me_3SiN(Me)OSiMe_3$ To Give the Corresponding Hemiaminal 2 and Nitrone 3 under Various Conditions

PhCHO + $Me_3SiN(Me)OSiMe_3$ → 2 (R = Ph; R′ = H) + 3 (R = Ph; R′ = H)

ratio, equiv	conditions (solvent, temp, time)	yield, % 2	3
1.0:1.0	PhH, 50 °C, 24 h	0	97
1.0:1.1	PhH, 50 °C, 16 h	21	79
1.0:2.0	PhH, 50 °C, 18 h	89	11
1.0:1.1	$CHCl_3$, 50 °C, 19 h	25	70
1.0:1.1	PhH, 50 °C, 24 h + SiO_2, 50 °C, 24 h	0	95

Scheme II



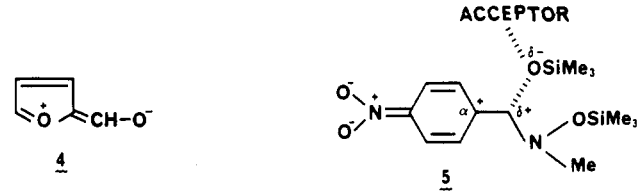
present. Table II lists detailed information on the formation of the hemiaminal and the nitrone of benzaldehyde under various reaction conditions.

The isolated hemiaminal 2 (R = Ph; R′ = H) proved to be stable when heated at 50 °C for 48 h in deuterated benzene.[5] However, in the presence of silica gel[6] (C_6D_6, 50 °C, 18 h), 2 (R = Ph; R′ = H) was converted almost quantitatively to the corresponding nitrone and hexamethyldisiloxane. More interestingly, when 0.05 equiv of benzaldehyde was added to the pure hemiaminal in benzene and the mixture was heated at 50 °C for 40 h, 42% conversion to the nitrone occurred.

We believe that benzaldehyde catalyzes the decomposition of the intermediate hemiaminal. When a large excess of 1 is present, all of the aldehyde is consumed quickly and is no longer available to effect nitrone formation. This leads to a buildup of the intermediate 2.

Consequently, we propose a bimolecular push–pull mechanism[7] to illustrate this phenomenon (see Scheme II). In effect, the carbonyl compound is acting as a Lewis acid,[8] i.e., trimethylsiloxide acceptor, while the hemiaminal is acting as a trimethylsiloxide donor.

It is also observed that in the cases where there is an electron-withdrawing or -donating effect on the carbonyl group (entries 2–4) the hemiaminal intermediates 2 do not decompose at an appreciable rate unless an acid catalyst is added. In the case of *p*-(dimethylamino)benzaldehyde, the dimethylamino group decreases the electrophilicity of the carbonyl carbon due to resonance.[9] This makes *p*-(dimethylamino)benzaldehyde a poor acceptor, though the corresponding hemiaminal should be a good donor. The same reasoning can be applied to 2-furaldehyde due to its canonical form 4.[10] For the case of *p*-nitrobenzaldehyde, the nitro group makes the α-carbon an electron-deficient center,[11] which is adjacent to a carbon bearing a partial positive charge in the transition state (see 5). Hence, the



silylated hemiaminal of *p*-nitrobenzaldehyde is a poor donor although *p*-nitrobenzaldehyde may be a good acceptor. Decomposition of 2 to the nitrone proceeds well only if there is a suitable balance between acceptor and donor. Addition of Me_3SiOTf overrides these effects, leading to the nitrone in high yields.

In addition to providing good-to-excellent yields,[12] this new method to generate *N*-methylnitrones possesses the following advantages: (1) Reactions can be carried out efficiently in aprotic solvents, which are superior to protic solvents for intramolecular 1,3-dipolar cycloadditions.[13] (2) Formation of the stable hexamethyldisiloxane as the byproduct drives the reaction to completion. This volatile material (bp 101 °C) is easily removed by rotary evaporation. (3) No aqueous workup is required and all nitrones are isolated directly in their unhydrated forms.[14] (4) Sequential [3 + 2] cycloaddition can be carried out in situ for both intra- and intermolecular cases[15] (entries 5 and 9[16]). In general, isolation of the nitrone is not necessary. (5) For most cases, only a stoichiometric amount of the aldehyde or ketone is required. (6) Under most circumstances, the reaction does not require external catalysts.

Although 1 reacts well with hindered aldehydes, such as trimethylacetaldehyde, one limitation is that it does not react appreciably with aromatic ketones. Acetophenone gave only a very small amount of the corresponding *N*-methylnitrone after 100 h.

Silylation of *N*-methylhydroxylamine leads to *N*-methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine. It has already been proven that the trimethylsilyl cationic species can serve as a "bulky proton", and its bulkiness can differentiate between carbonyl groups on the basis of steric

(5) The reaction was run in deuterated benzene to allow direct observation of hexamethyldisiloxane by NMR.

(6) Silica gel (63–200 μm, E. Merck 7734) acts as a mild acid catalyst.

(7) (a) Swain, C. G. *J. Am. Chem. Soc.* **1950**, *72*, 4578. (b) Gould, E. S. "Mechanism and Structure in Organic Chemistry"; Holt, Rinehart and Winston: New York, 1959; p 299.

(8) (a) VanderWerf, C. A. "Acids, Bases and the Chemistry of the Covalent Bond"; Reinhold: New York, 1961; Chapter 5. (b) Ho, T.-L. "Hard and Soft Acids and Bases Principle in Organic Chemistry"; Academic Press: New York, 1977; Chapter 7.

(9) Chuchani, G. In "Chemistry of Functional Groups: The Chemistry of the Amino Group"; Patai, S., Ed.; Interscience Publishers: New York, 1968; Chapter 5.

(10) Dean, F. M.; Sargent, M. V. In "Comprehensive Heterocyclic Chemistry"; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol. 4, Chapter 10, Part 3.

(11) (a) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; p 247. (b) Urbanski, T. In "The Chemistry of Functional Groups: The Chemistry of the Nitro and Nitroso Groups"; Feuer, H., Ed.; Interscience Publisher: New York, 1970; Part 2, Chapter 2.

(12) The isolated yields of nitrones are in all cases comparable or much higher than those reported in the literature (see Table I).

(13) Petersen, P. R. Ph.D. Dissertation, Wayne State University, Detroit, MI, 1977.

(14) Our observed melting points are consistent with those of the known unhydrated nitrones in the literature. For references, see: (a) Goldschmidt, H.; Zanoli, E. *Chem. Ber.* **1812**, *25*, 2573. (b) Brady, O. L.; Dunn, F. P.; Goldstein, R. F. *J. Chem. Soc.* **1926**, 2386.

(15) One additional intermolecular [3 + 2] cycloaddition involved the in situ reaction of *N*-methyl-α-phenylnitrone with dimethyl maleate. A mixture of diastereomeric isoxazolidines was obtained in 85% yield.

(16) In the literature, this reaction was performed with the isolated nitrone and phenyl isocyanate.

hindrance.[17] Use of 1 to prepare mononitrones from compounds bearing two or more carbonyl groups by applying the bulky proton concept will be investigated in due course.

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(18) (a) Abou-Gharbia, M.; Joullie, M. M. *Synthesis* **1977**, 318. (b) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047.
(19) Stamm, H.; Hoenicke, J. *Justus Liebigs Ann. Chem.* **1971**, *748*, 143.
(20) LeBel, N. A.; Whang, J. J. *J. Am. Chem. Soc.* **1959**, *81*, 6334.
(21) Moderhack, D.; Lorke, M. *J. Chem. Soc., Chem. Commun.* **1977**, 831.
(22) Exner, O. *Collect. Czech. Chem. Commun.* **1951**, *16*, 258.
(23) Schenk, C.; Beekes, M. L.; van der Drift, J. A. M.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 278.

Additions and Corrections

Vol. 49, 1984

Amos B. Smith, III* and Andrew S. Thompson. An Enantioselective Total Synthesis of (−)-Talaromycins A and B.

Page 1470. Structures **15b** and **17** were drawn with the incorrect absolute configuration: **15b** should have the configuration 4*S*,6*R*,9*R* (talaromycin numbering) and **17** the 6*R*,9*R* configuration.

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Masahiro Hirama,* Takeshi Noda, and Shô Itô*. Convenient Synthesis of (*S*)-Citronellol of High Optical Purity.

Page 128. The optical rotation of synthetic (*S*)-(−)-citronellol is miscalculated. It should be corrected as $[\alpha]^{18}_{D}$ −5.44° (neat). Consequently, the footnote 7 should be deleted. The correct rotation we obtained is the highest of those reported for citronellol irrespective of enantiomers. In addition, we have recently proved that (*R*)-(+)-1-(1-naphthyl)ethylamine (Aldrich Chemical Co.) used for the determination of the optical purity contains 1.7 ± 0.3% of *S* enantiomer. Therefore, the optical purity of our synthetic (*S*)-citronellol should be higher than 99%.